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(56) Documents cited
GB 1430324
GB 1411432
GB 0872893
GB 0790605
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(54) Antimycotic preparations in a cream or ointment base

(57) Antimycotic therapeutic preparations contain one or more antimycotically active substances and urea in a cream or ointment base. The antimycotic can be i.e. an antibiotic, a quinoline or imidazole derivative.

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SPECIFICATION

Antimycotic preparations with a cream or ointment base

The invention relates to antimycotic preparations with an ointment or cream base which are particularly suitable in the treatment of dermatophytes.

Fungal infections are caused by numerous different types of microscopically small fungi which may be parasites, for example, living on or in living animal tissue. Fungal organisms which attack the skin, hair and nails are known as dermatophytes. Numerous pathogenic varieties of yeast fungus are also known. A distinction is drawn between non-pathogenic fungal growth on the skin and pathogenic phenomena, which may take the form, for example of skin discoloration and dermatomycosis. The dermatophytes include, for example, *Erythrasma, Epidermophyton, Favus, Microsporum, Sporotrichum* and *Trichophyton* fungi and the pathogens which cause pityriasis versicolor. Piedranigra and trichomycosis palmellina are typical fungal scalp infections. The objective when treating fungal infections is to eliminate the parasitic fungi from the tissue attacked and to clear up the symptoms.

The fight against fungal diseases entered a new stage with the development of antibiotics. Antibiotics may be taken internally but may also be applied locally as constituents of ointments, powders, and solutions. In modern thereby, the antibiotics griseofulvin, nystatin, amphotericin B, pimaricin and trichomycin, in particular, are used locally. Antimycotic active substances also include carbonic acid derivatives and aliphatic carboxylic acids (especially those with fairly long carbon chains) and derivatives thereof (e.g. caprylic acid, undecenylic acid, dithiocarbamate, thiourea and thiocyanates); aromatic carboxylic acids and the amides thereof (benzoic acid, salicylic acid, salicylic acid amide and anilide); phenols and cresols, primarily as antifungal disinfectants (hexylresorcinol, hexachlorophene); aromatic sulphides, polysulphides and sulphoxides (5,5-dichloro-2,2-dihydroxydiphenylsulphide); invert soaps (quaternary ammonia and phosphonium compounds, decamethylene-bis-(4-thio-pyridine-methyl-tosylate); quinoline derivatives (8-hydroxyquinoline sulphate, halogenated quinolines, 7-iodo-8-hydroxy-quinoline-5-sulphonic acid, 5-chloro-7-iodo-8-hydroxy-quinoline, 5-chloro-8-hydroxy-quinoline, 5,7-dichloro-8-hydroxyquinaldine, 5,7-diiodo-8-hydroxyquinoline and decamethylene-bis-[4-amino-quinaldinium chloride]); organometallic compounds; (organic mercury compounds such as phenyl mercury borate, chloride, nitrate, etc; N^1-ethyl mercury (II)-N^1-acetylsulphanilamide; organic copper, zinc, antimony and bismuth compounds); benzothiazole derivatives (2-dimethylamino-6-(β-diaminoethoxy)-benzothiazole dihydrochloride); imidazole derivatives: [1-(o-chloro-α,α-diphenyl-benzyl)-imidazole, 1-[o,p-dichloro-β-(o,p-dichlorobenzyloxy)-phenethyl]imidazole]; benzimidazole derivatives; [2-phenylbenzimidazole, 2-furfurylbenzimidazole]; thiadizine derivatives: [3,5-dibenzyl-tetrahydro-1,3,5-thiadizine-2-thione]; furan derivatives: [5-nitro-2-furfuryl-3-chloropropionate]; quinones: [tetrachloro-p-benzoquinone, 1,4-naphthoquinone, phenanthraquinone]; sulfphonamides and sulphones; aromatic diamidines: [2-hydroxystilbamidine, diamidinodiphenylamine]; and dyes (triphenylmethane dyes, brilliant green, malachite green, gentian violet) (cf. Ullmanns Encyclopädie der Techn. Chemie 4th edition, volume 10, pages 36—37, Verlag Chemie and 3rd edition, volume 14, pages 1—11, Verlag Urban & Schwarzenberg).

Suitable forms for administration include powders, mixtures to be shaken, oils, ointments, creams, pastes and gels. The effective penetration into the skin of an active substance increases according to its form in the following order: powder, mixture to be shaken, paste, ointment. Forms for administration prepared using emulsions (emulsified ointments and creams) as well as anhydrous ointments, are, in particular, used in dermatotherapy.

Ointment bases and emulsifiers are described, for example, in Ullmanns Encyclopädie der Technischen Chemie, 3rd edition, volume 10, pages 683—688, volume 4, pages 33—37. By using emulsified ointments as a form for administration it is possible to adapt the ointment to the individual needs of the skin or to the specific conditions for the resorption of the active substance incorporated therein by a suitable combination of basic substances and emulsifier. Generally, water-soluble active substances are used in oil-in-water emulsions and fat-soluble active substances are used in water-in-oil emusions. The fat content in emulsified ointments may vary from being high in fat to fat-free. Examples of suitable ointment bases for anhydrous ointments include paraffin hydrocarbons (such as Vaseline, paraffin), and animal and vegetable waxes and fats (adeps suillus, adeps lanae, hydrogenated ground nut and palm kernel oil, silicone oils and esters of higher molecular natural fatty acids and polyethylene oxides with a molecular weight of from 300 to 3000 in admixture).

A prerequisite for the effectiveness of active substances is that they reach the desired site. When creams and ointments are used for the treatment of skin complaints, this generally means that the active substances must be able to penetrate sufficiently into the skin. The uppermost layer of the skin, namely the horny layer (stratum corneum) consisting of epidermal cells, with its low water content, constitutes a barrier to penetration, i.e. the horny layer makes it difficult for active substances to penetrate into the skin, penetration depending to some extent on the nature of the active substances. The effect of a hydrophilic active substance, such as an invert soap, for example, is restricted to the surface of the skin, whereas lipophilic active substances such as the phenols and cresols, for example, can be resorbed rather more easily (and may thus bring about a systemic/toxic effect in the organism).

In the epicutaneous application of antimycotic active substances, the intended site is in the

region of the surface of the skin. Therefore, there would be no point in improving resorption through the skin, for example by hyperaemia-inducing measures or by the use of entrainers (e.g. DMSO). Substances which loosen the horny layer of the skin and thus facilitate penetration of active substances include urea. The increased penetration of various active substances applied to the skin which is brought about by urea immediately leads to the problem that these active substances penetrate the skin so rapidly that either they do not have any effect or they pass into the circulation and lead to systemic side-effects.

There is therefore a need to increase the retention time in the superficial areas of the skin of antimycotic therapeutic preparations applied to the skin. We have now found that antimycotic therapeutic preparations with a cream or ointment base provide a longer retention time for the active substances in the skin, particularly in the surface regions, if urea is applied at the same time. Contrary to all expectations, the simultaneous action of urea does not increase the speed of penetration of antimycotic active substances through the skin but, rather, delays such penetration.

From the therapeutic point of view, the effect observed is of considerable benefit since the antimycotics in question can act longer on the fungi present in the skin. This results in increased effectiveness of the antimycotics. Moreover, it opens up the possibility of extending the intervals between applications. Furthermore, the risk of systemic side-effects (such as those which have already been indicated with reference to phenols and cresols) is reduced.

We therefore provide antimycotic preparations comprising one more antimycotically active substances and urea in a cream or ointment base.

The preparations according to the invention may be applied in both human and veterinary medicine.

The antimycotic substances used may be, in particular, any of those already mentioned above. Preferred are the polyene antibiotics amphotericin B, nystatin and pimaricin, griseofulvin, the quinoline and imidazole derivatives, tolnaftate and haloprogin. Another preferred embodiment of the invention is the combination of the preparations according to the invention with glucocorticosteroids.

The ointment base or cream used may be one of those known from the prior art. Those which are preferred are oil-in-water or water-in-oil emulsion systems which affect the natural water/lipid balance of the skin as little as possible but due to the solubility of active substances in the two-phase system promote the satisfactory penetration of these active substances into the site of activity.

The ointments or creams may also be prepared in a manner known *per se*, for example by mixing a lipid phase with an emulsifier having a lower HLB (Hydrophilic Lipophilic Balance) value and the aqueous phase with an emulsifier having a high HLB value at a temperature which is above the phase inversion point under the effect of high shearing forces and then stirring the components when cold, so as to form a stable two-phase fat/water system containing a complex emulsifier.

Generally, the urea content is from 5 to 30% by weight, preferably from 10 to 15% by weight, based on the spreadable preparation.

The urea may advantageously be introduced either by distributing the urea in water, optionally with other buffer systems such as betain/lactic acid, dissolved in an oil-in-water base, or by introducing it, suitably stabilised in a water-in-oil emulsion. Stabilisation should minimise the reaction of addition of the urea to form ammonia and carbon dioxide.

The following Examples serve to illustrate the antimycotic preparation according to the invention, without restricting the scope of the protection sought therefor.

1st Example

A hydrophobic phase, consisting of

Vaseline	28 g
isopripylmyristate	10 g
hard fat	3 g

is melted at about 70°C until clear.

At a temperature of from 50 to 60°C,

sorbitan monolaurate	2 g

is stirred in, and at 40 to 55°C the aqueous phase, consisting of a mixture of

water	17 g
urea	15 g
sorbitol	1 g
polyoxyethylene fatty acid ester	5 g

can be incorporated in the hydrohobic phase. In order to stabilise and control the consistency of the mixture,

microcrystalline cellulose	19 g

is dispersed therein.

2nd Example

A mixture is prepared from

water	5.6 g
glycerol	20 g
urea	15 g.

At 70 to 85°C,

glycerol	35 g
Stenol 16/8	9.9 g
Lanette ES	1.5 g
Cetiol V	3.0 g

are melted with stirring and homogenised.

When this has cooled to 60°C, the urea-containing mixture and the active substance

p-aminophenyl sulphonamide	10.0 g

are added thereto.

Stenol 16/8 is a long chain fatty acid ester with medium to long-chain fatty alcohols, particularly oleyloleate. Lanette ES is a mixture of cetylstearylalcohol with cetylstearylsulphate. Cetiol V is a mixture of saturated C_{16}—C_{18} alcohols based on animal fats and oils.

By analogy with Examples 1 and 2, preparations containing amphotericin B, nystatin, pimaricin, griseofulvin, quinoline derivatives, hexachlorophene, imidazole derivatives such as clotrimazole or miconazole, tolnaftate or haloprogin may be prepared.

3rd Example

A hydrophobic phase, consisting of

Vaseline	26 g
isopropylmyristate	10 g
hard fat	3 g
clotrimazole	1 g

is melted at about 70°C until clear.

At a temperature of 50°C,

sorbitan monolaurate	2 g

is stirred in, and at 40 to 55°C an aqueous phase, consisting of a mixture of

water	16 g
urea	15 g
sorbitol	1 g
polyoxyethylene fatty acid ester	5 g

can be incorporated in the hydrophobic phase. In order to stabilise and control the consistency of the mixture,

microcrystalline cellulose	19 g

is dispersed therein.

4th Example

A hydrophobic phase, consisting of

Vaseline	28 g
isopropylmyristate	10 g
hard fat	3 g

is melted at about 70°C until clear, and

econazole nitrate	1 g

is dispersed therein.

At a temperature of from 50 to 60°C

sorbitan monolaurate	2 g

is stirred in, and at 40 to 55°C an aqueous phase, consisting of a mixture of

water	16 g
urea	15 g
sorbitol	1 g
polyoxyethylene fatty acid ester	5 g

can be incorporated into the hydrophobic phase. In order to stabilise and control the consistency of the mixture

rice starch	19 g

is dispersed therein.

5th Example

A mixture of

polyoxyethylene fatty acid ester	6 g
cetyl alcohol	1 g
stearic acid	3 g
paraffin liquidum	2 g
wool wax alcohol	1 g
triglyceride fatty esters	2 g
miconazole nitrate	2 g

is liquefied at 70°C and is homogenized. At 55 to 60°C this homogenate is dispersed into an aqueous phase, consisting of

propylene glycol	2 g
glycerine	1.5 g
citric acid	0.1 g
urea	12 g
water	67.4 g

and the mixture is homogenized until the desired consistency is reached.

6th Example

A mixture of various types of polyethylene glycol, having average molecule weights of 300, 1500 and 3000, and using 28 g of each type, is melted until clear.

Whilst cooling,

undecanoic acid	5 g
dichlorophen	1 g
5-chloro-8-hydroxy-quinoline	10 g

is dispersed therein.

7th Example

A mixture of

Vaseline	15 g
solid fat	5 g
glycerin tribehenate	25 g

is melted at about 70°C until clear.

At a temperature of from 45 to 55°C, a mixture of

urea	10 g
corn starch	14 g
miconazole nitrate	2 g

is dispersed therein.

After cooling of the mixture to 30°C, a suspension of

hydrocortisone	1 g in
isopropylmyristate	20 g
sorbitan monolaurate	3 g
polyoxyethylene fatty acid ester	5g

is added thereto and the mixture is cooled as quickly as possible.

Claims

1. Antimycotic preparations comprising one or more antimycotically active substances and urea in a cream or ointment base.

2. A preparation as claimed in claim 1, which contains urea in an amount of from 5 to 20% by weight, based on the total weight of preparation.

3. A preparation as claimed in claim 1, which contains urea in an amount of from 10 to 15% by weight, based on the total weight of the preparation.

4. A preparation as claimed in any of claims 1, 2 or 3, wherein the active substance is amphotericin B.

5. A preparation as claimed in any of claims 1, 2 or 3, wherein the active substance is nystatin.

6. A preparation as claimed in any of claims 1, 2 or 3, wherein the active substance is pimaricin.

7. A preparation as claimed in any of claims 1, 2 or 3, wherein the active substance is griseofulvin.

8. A preparation as claimed in any of claims 1, 2 or 3, wherein the active substance is a quinoline derivative.

9. A preparation as claimed in any of claims 1, 2 or 3, wherein the active substance is an imidazole derivative.

10. A preparation as claimed in any of claims 1, 2 or 3, wherein the active substance is tolnaftate.

11. A preparation as claimed in any of claims 1, 2 or 3, wherein the active substance is haloprogin.

12. A preparation as claimed in any of claims 1 to 11, which additionally includes a glucocorticosteroid.

13. An antimycotic preparation substantically as hereinbefore described with reference to any of the Examples.

14. A method of topical treatment of the human or animal body to combat fungal infections which method comprises administering topically to the said body an effective amount of an antimycotic preparation as defined in any one of the preceding claims.

15. An antimycotic preparation as claimed in any one of claim 1 to 13 for use in the topical treatment of fungal infections of the human or animal body.

16. Each and every novel compound, composition and method herein described.

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